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Effect of Chlordimeform (A Formamidine Pesticide) on Schedule-Controlled Responding of Pigeons

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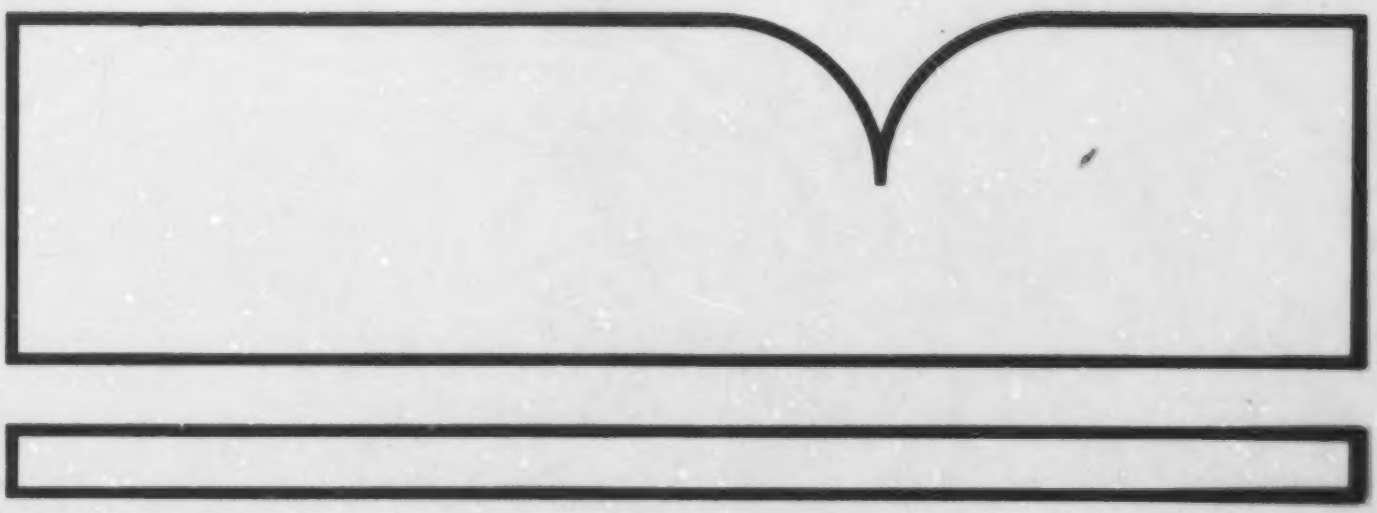

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16. ABSTRACT

The formamidines are a relatively new class of pesticides which are effective against mites, ticks, and other insects [8,15]. Chlordimeform, a representative of this class, is of great toxicological interest because it is effective against pests which are resistant to organophosphate and carbamate pesticides [3]. Likewise in birds and mammals, chlordimeform produces symptoms of toxicity which are different from those produced by organophosphate and carbamate pesticides [5].

In terms of biochemical effects, chlordimeform has been shown to inhibit monoamine oxidase which increases brain levels of norepinephrine and serotonin [1]. This effect has been interpreted as the action by which chlordimeform produces the symptoms characteristic of the "serotonergic syndrome" [20], a behavioral pattern consisting of forepaw treading, head weaving, hind limb abduction, rigidity, Straub tail, and tremor. However, other biochemical effects of chlordimeform have also been noted. Chlordimeform has actions similar to local anesthetic agenst [2,18]; it inhibits prostaglandin sysnthesis [23], and in the firefly, is an agonist at octopamine receptors [9].

Because of the paucity of studies on the behavioral effects of chlordimeform, and the diversity of biochemical effects reported, the present studies were initiated. The pigion was selected for experimental study because of the extensive use of the pigeon in in characterizing the behavioral effects of drugs and toxicants affecting the central nervous system [16] and the need for a comparative neurotoxicology in the assessment of a pesticide's impact on the environment [13].

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Effect of Chlordimeform (A Formamidine Pesticide) on Schedule-Controlled Responding of Pigeons

J. DAVID LEANDER[1] AND ROBERT C MACPHAIL[2]

[1]*Department of Pharmacology, School of Medicine 231H, University of North Carolina at Chapel Hill, Chapel Hill, NC 27514*
and
[2]*Neurotoxicology Division, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711*

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LEANDER, J. D. AND R. C. MACPHAIL. *Effect of chlordimeform (a formamidine pesticide) on schedule-controlled responding of pigeons*. NEUROBEHAV. TOXICOL. 2(4) 315–321, 1980.—The effects of chlordimeform, a formamidine pesticide, were studied on key peck responding maintained by a multiple fixed-ratio, fixed-interval schedule of food presentation. In general, acute intramuscular injections (0.625–40 mg/kg) of chlordimeform decreased rates of responding under the fixed-interval component at lower doses than those which decreased rates of responding in the fixed-ratio component, with complete behavioral suppression following 20–40 mg/kg. Fixed-interval patterning was disrupted in a dose-related fashion. Orally administered doses (5, 10, and 20 mg/kg) were equipotent with intramuscular doses in decreasing rates of responding. Daily intramuscular injection of 10 or 20 mg/kg of chlordimeform produced tolerance to chlordimeform's behavioral suppressing effects, but not to its effects on fixed-interval patterning.

Chlordimeform Tolerance Behavior Pigeon

THE formamidines are a relatively new class of pesticides which are effective against mites, ticks, and other insects [8,15]. Chlordimeform, a representative of this class, is of great toxicological interest because it is effective against pests which are resistant to organophosphate and carbamate pesticides [3]. Likewise in birds and mammals, chlordimeform produces symptoms of toxicity which are different from those produced by organophosphate and carbamate pesticides [15].

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METHOD

Animals

Four male White Carneaux pigeons (Palmetto Pigeon Plant, Sumter, SC) were used. All birds had several months of training under the multiple schedule of food presentation and with injections of distilled water (one bird, no. 1413, also had 3 injections of scopolamine) prior to inclusion in this study. The birds were maintained at 80% of their free-feeding weight by the pigeon grain (Ralston Purina Top Flight Pigeon Grain) presented during experimental sessions and by postsession supplemental feedings. The pigeons were individually housed in wire mesh cages. Water and oyster shell grit were continuously available in the home cage of the birds. Water was also available during the experimental sessions.

Apparatus

The experimental chambers were sound-attenuating and ventilated [4]. The experimental space was 29 cm high × 27 cm wide × 29 cm long. A translucent plastic response key, 2 cm in diameter, was mounted in the center of a wall inside the chamber, 22 cm above the wire mesh floor. The response

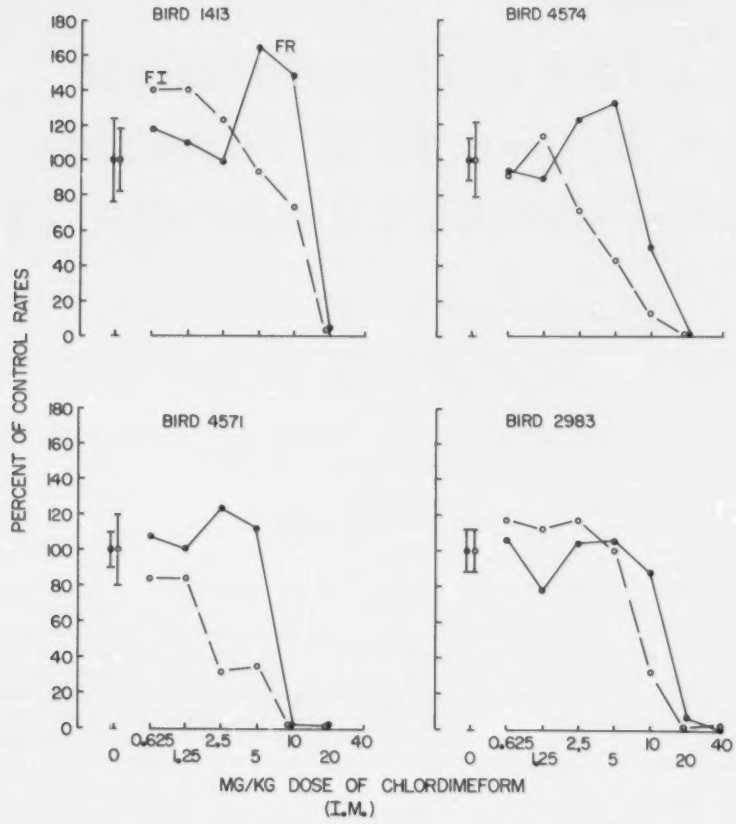

FIG. 1. Effects of chlordimeform administered intramuscularly on the rates of responding under each component of the multiple FR FI schedule of grain presentation for individual birds. The data are plotted as percent of the control values. The brackets at 0 show ± 1 SD around the control mean. Filled circles show the effects on FR-component performance and unfilled circles show the effects on FI-component performance. Each point represents the mean of two or more determinations. Control FR and FI rates, respectively, for bird 1413 are 3.10 and 0.64 responses/sec; for bird 4574, 4.41 and 1.42; for bird 4571, 3.55 and 0.86; and for bird 2983, 2.29 and 0.92.

key could be transilluminated by red or blue lights. A peck with a minimal force of 0.15 N operated the key and defined the response. Below the response key was a rectangular opening through which the pigeon could be given access to mixed grain. The experimental space was illuminated by a 7.5 W bulb. During the 4-sec grain presentation cycle, all lights in the test chamber were off except one illuminating the grain. Relay programming and recording equipment in an adjacent room controlled the events and recorded the data.

Procedure

The multiple fixed-ratio 30 response, fixed-interval 5-minute schedule (mult FR-30, FI-5) can be described in the following manner [4]. When a blue light transilluminated the response key, the 30th response produced the 4-sec grain presentation (FR-30). When a red light transilluminated the response key, the first response to occur after 5 min elapsed produced grain presentation (FI-5). A 40-sec limited hold was in effect in both components; i.e., in the FR component, the bird had 40 sec to emit the 30 responses, and in the FI component, the bird had up to 40 sec after 5 min had elapsed to respond and produce grain presentation. Schedule components alternated after each grain presentation or when the limited hold elapsed. Sessions were conducted Monday through Friday for 1 hr each day and began with the FR component (12 FR and 12 FI components in each session).

Administration of Chlordimeform

Chlordimeform HCl (99+% pure, obtained from Noram Agricultural Products, Inc., Woodstock, IL 60098) was dissolved in a 0.9% saline solution and administered in a volume of 1 ml/kg of body weight 10 minutes before the test session. For the studies of chlordimeform's effects after

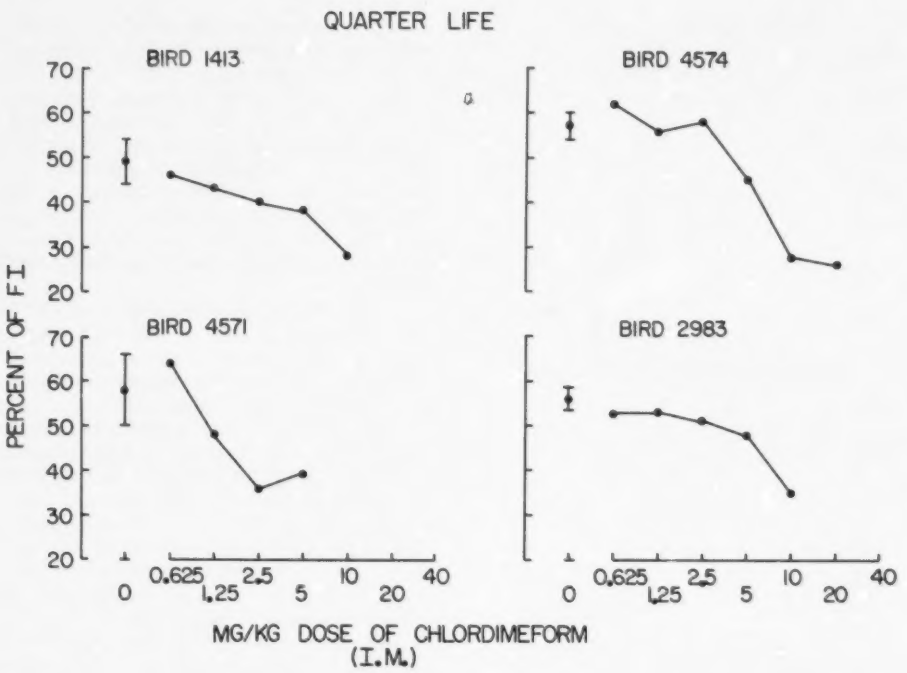

FIG. 2. Effects of chlordimeform administered intramuscularly on the quarter-life measure of response patterning during the FI component. The mean ± 1 SD are shown at 0. The quarter-life would be 25% of the FI if responding occurred at a constant rate through the FI. Quarter-life values of greater than 25% indicate that responding occurred in a positively-accelerated pattern in the FI. Quarter-life values are not calculated for FI rates below 0.1 response/sec.

intramuscular injections, the injections were made into the pectoral muscle of the pigeon. For the studies of the oral route of administration, the chlordimeform doses were administered by passing an 18 cm long feeding needle down the throat and through the crop to the opening of the proventriculus. Because chlordimeform has been shown to be rapidly metabolized and eliminated after oral administration in the rat [11], it was usually administered twice weekly. Thus during determination of acute dose-effect curves in which each animal received a different sequence of dose determinations, chlordimeform doses were usually administered before the Tuesday and Friday sessions, whereas saline control vehicle (1 ml/kg) was administered on Thursdays. The data obtained from Thursdays serve as control data for the evaluation of chlordimeform's effects. During the tolerance study, chlordimeform was administered daily, though testing did not occur on weekends.

Measurement of Effects

Average rates of responding during the FR and FI components were computed in responses per second from digital counters and elapsed-time meters. Also, from the total number of responses recorded in each tenth of the FI duration, the percent of the interval taken for the first quarter of the total responses to occur was determined. This FI quarter-life value provides an indication of the temporal patterning of responding which is independent of the rate of responding [5].

In interpreting the effects of chlordimeform in individual birds, data which exceeded ± 2 SD of the control mean were considered "significant". Each dose of chlordimeform was administered at least twice in random order to each bird during the determination of the acute dose-effect curves.

RESULTS

Under the FR component of the multiple schedule, a high rate of responding occurred (2.3–4.4 responses/sec), whereas under the FI component, lower average rates were produced (0.64–1.75 responses/sec in individual birds). Responding under control conditions in the FI component was characterized by a pause and then a positively accelerated pattern of responding throughout the FI. This was shown by the baseline quarter-life values in that 50–60% of the FI elapsed before the first quarter of the total responses occurred. In the figures, the effects of chlordimeform on rates of responding are shown as percent of the control values.

Figure 1 shows the effects of a range of chlordimeform doses administered intramuscularly on the rates of responding in both components of the multiple FR FI schedule. In all 4 birds, chlordimeform decreased rates of responding in the FI component at lower doses than those which decreased

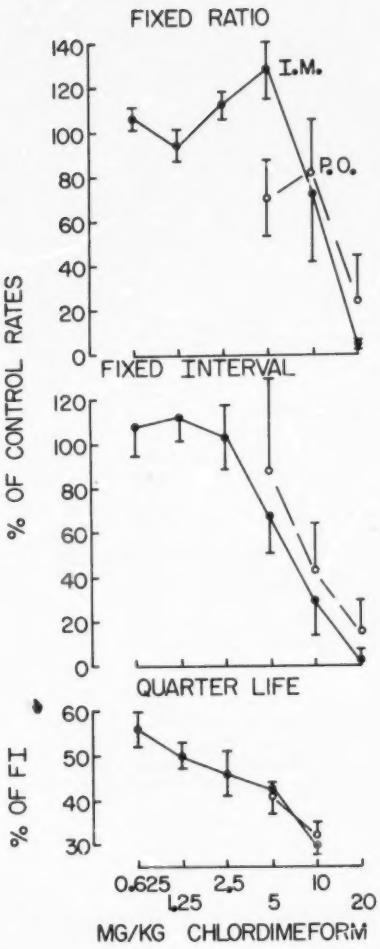

FIG. 3. Comparison of intramuscularly and orally administered chlordimeform on the rates of responding in the FR component (top graph), FI component (middle graph) and on the quarter-life value of the FI component. Each point is the mean ± 1 SEM of the values obtained in 4 birds. Filled circles show the effects of intramuscularly administered chlordimeform, whereas the unfilled circles show the effects of orally administered chlordimeform.

rates of responding in the FR component. This effect is most clearly seen with birds 4571 and 4574; chlordimeform doses of 2.5, 5, and 10 mg/kg decreased the FI rates without affecting, or in some instances increasing, the FR rates of responding from non-drug control levels. In one bird (4571), 10 mg/kg produced a near zero level of responding in both components, whereas in the other three birds, 20 mg/kg was required to produce a comparable behavioral suppression. Only doses which produced complete suppression of schedule-controlled responding exhibited overt signs of intoxication (e.g., sedation). In bird 1413, low doses (0.625 and 1.25 mg/kg) significantly increased mean rates of responding in the FI components.

Figure 2 shows the effects of i.m. chlordimeform on the patterning of responding in the FI component as measured by the quarter-life value. Under untreated conditions, the quarter-life values for individual birds ranged between 45 and 60% of the FI. With chlordimeform there is a dose-related decrease in quarter-life values in all birds. This means that as a function of increasing dose, responding throughout the FI tended to become constant, and FI responding lost its characteristic positively accelerated pattern. This was accomplished by both increasing the low rates of responding early in the FI and decreasing the high terminal rates.

Figure 3 compares the effects of chlordimeform after intramuscular injection to those after oral intubation. In terms of response-rate suppression as well as quarter-life decreases, there was little difference between the two routes of administration of chlordimeform.

Figures 4 and 5 show the effects of daily administration of chlordimeform on rates of responding and quarter-life values, respectively, for 3 pigeons. As measured by a return of responding to control levels, tolerance developed rapidly, with all three birds exhibiting almost complete recovery of rates of responding within 4 days of daily treatment (Fig. 4). Just as there was a tendency for the FR rates of responding to be suppressed less than the FI rates during the acute dose-effect determinations (Fig. 1), tolerance appeared to develop more rapidly in the FR component than in the FI component. During the second week of daily administration, FI rates for bird 1413 were elevated often markedly compared to control levels during this time. The points to the far right in Fig. 4 show that some tolerance was lost after 3 weeks without chlordimeform, and there was a greater tolerance loss in the FI component than in the FR component.

Though the data in Fig. 4 show that tolerance occurred to the effects of chlordimeform on average rates of responding, the data in Fig. 5 show that tolerance does not occur to chlordimeform's effect on the patterning within the FI. Even though rates of responding within the FI recovered to control levels, or above, with daily administration of chlordimeform, the quarter-life values remained well below non-drug control levels.

DISCUSSION

The present studies have shown that chlordimeform produced behavioral effects on the schedule-controlled behavior of pigeons at doses which are markedly lower than those reported to produce lethality in rats. In the present studies, almost complete behavioral suppression occurred and overt signs of sedation were apparent after doses of 20 mg/kg were administered either by the intramuscular or oral route. These effects were produced by doses well below the LD-50 in the rat after intraperitoneal injection, which has been reported from 123 mg/kg [21] to approximately 300 mg/kg [8]. In one pigeon (No. 1413), increases in rate of responding occurred at doses as low as 0.625 mg/kg, whereas doses of 2.5 and 5 mg/kg clearly affected the performance of all birds. These effects occurred in the same dose range in which chlordimeform increases feeding in non-food-deprived rats [19] and flavor aversions to saccharin are produced in rats [14]. All of these studies indicate that there are significant behavioral effects of chlordimeform at doses well below levels considered to be toxic to mammals and birds. The present results also show that there is little difference be-

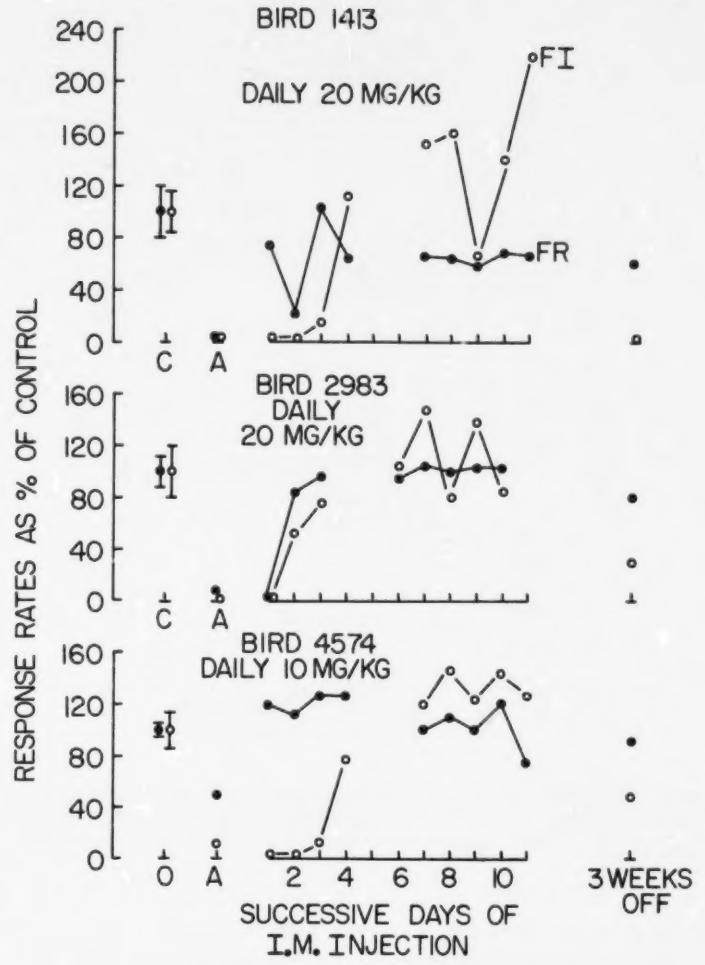

FIG. 4. Effects of daily administration of chlordimeform on the rates of responding under each component of the multiple schedule for individual birds. Filled circles show the effects on the rate of responding in the FR component and unfilled circles show the effects on the FI rates. The points and brackets at 0 show the mean ± 1 SD of the intramuscular control rates. Points at A indicate the effects of the doses shown during the determination of the dose-effect curve in Fig. 1. Birds 1413 and 2983 received 20 mg/kg of chlordimeform daily, whereas bird 4574 received 10 mg/kg of chlordimeform daily. These were the minimal doses for near-zero levels of responding in these birds (Fig. 1). The successive days without points were weekends on which the birds were injected but not tested. The points at the far right ("3 weeks off") show the effects of the same dose of chlordimeform after these birds had not received chlordimeform for 3 weeks.

tween intramuscular and oral routes of administration of chlordimeform in suppressing behavior motivated by food presentation.

Chlordimeform in the present study produced greater suppression of responding in the FI component than responding in the FR component. This effect has not previously been reported for the pesticides, but has been reported for acute doses of some antipsychotics [12], barbiturates and ethanol [10] in the pigeon. Thus chlordimeform in low doses produces effects like the antipsychotic or antianxiety agents on schedule-controlled responding, rather than like the local anesthetics [17] as might have been predicted on the basis of toxic effects found after higher doses, e.g. convulsions and cardiovascular collapse [18]. Also, increased feeding in rats [19] following chlordimeform is similar to the findings with the benzodiazepine antianxiety agents [22].

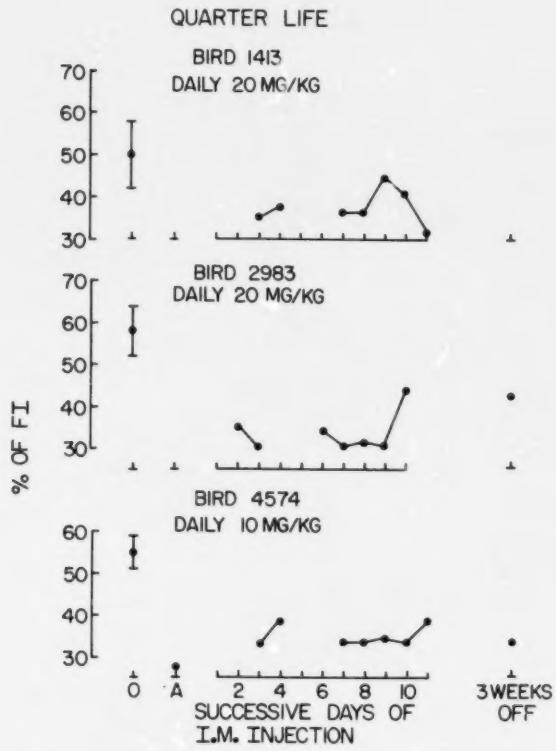

FIG. 5. Effects of daily administration of chlordimeform on the quarter-life value of the FI component for individual birds. Details are as with Fig. 4. Quarter-life values were not calculated for sessions where the FI rate was below 0.1 response/second.

The data showing tolerance in the present study also support a tentative hypothesis of a similarity in behavioral action of chlordimeform and the benzodiazepines. Unpublished data from this laboratory have shown that chronic administration of the benzodiazepine diazepam, produces a rapid tolerance in the pigeon to its effects on schedule-controlled performance.

The research on chlordimeform indicates the need for further studies of the behavioral effects of chlordimeform and related formamidines in the assessment of environmental impact of these pesticides. The behavioral studies suggest that chlordimeform produces effects similar to those of the benzodiazepine antianxiety agents. These effects should not be considered lightly in view of the problems associated with the benzodiazepines, such as sedation, tolerance, physical dependence, and interactions with psychoactive drugs [6,7].

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